



# **The public health risks of bacterial strains producing ESBLs and/or AmpC beta-lactamases in food and food-producing animals**

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# Terms of Reference

1. To **propose a definition** of the ESBL and/or AmpC producing bacterial **strains and genes** relevant for PH and linked to FP-animals or food borne transmission.
2. To **review** the information on the **epidemiology** of R to broad spectrum cephalosporins, in FP-animals and foods.
3. To **analyse the methods for detection** (isolation and identification) and **characterisation** of ESBL and/or AmpC-producing bacteria, encoding genes and associated mobile elements.
4. To make **recommendations** for a **harmonised monitoring** of R caused by ESBL and/or AmpC in food and FP-animals and food.
5. To **identify risk factors** contributing to the occurrence, emergence and spread of ESBL and/or AmpC producing bacterial strains in FP-animals and food.
6. To **identify and rank possible control options**, considering their efficiency in reducing PH risk. Advantages and disadvantages of different options.

# Background to PH threat

- Many community and hospital-acquired infections are caused by bacteria that are no longer sensitive to 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> generation cephs
- Infections with such resistant organisms are associated with poorer patient outcomes, increased morbidity, mortality, increased length of stay and increased costs
- There has been a steady increase in the rates of invasive *E. coli* and *K. pneumoniae* isolates that are resistant to 3<sup>rd</sup> generation cephs since 2000 (EARNs-Net)
- Although person-to-person spread is recognised as the main method of spread of ESBL/AmpC- $\beta$ -lactamase-containing *E. coli* both in hospitals and the community, the primary reservoirs of such organisms are contentious.
- ESBL-producing *E. coli* have been isolated from FP-animals and derived foods in many European countries (particularly poultry and cattle). This has raised questions about the possible role of animal- and food-related reservoirs on this phenomenon

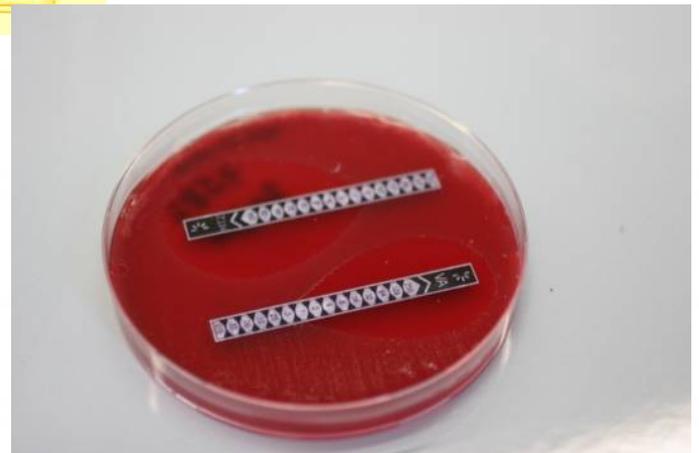
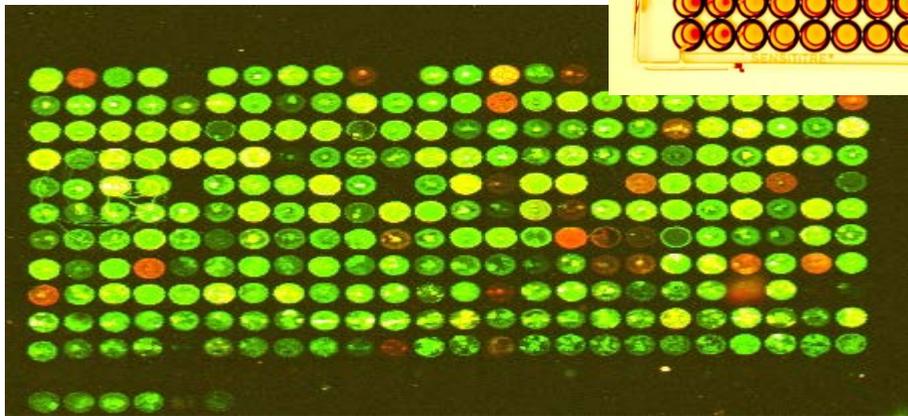
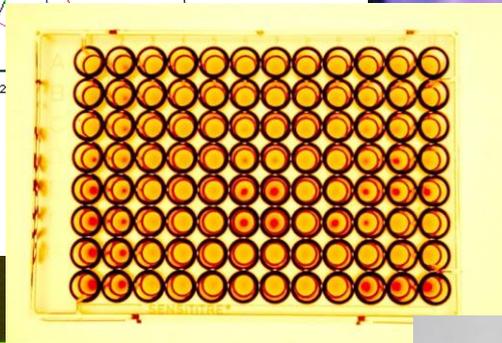
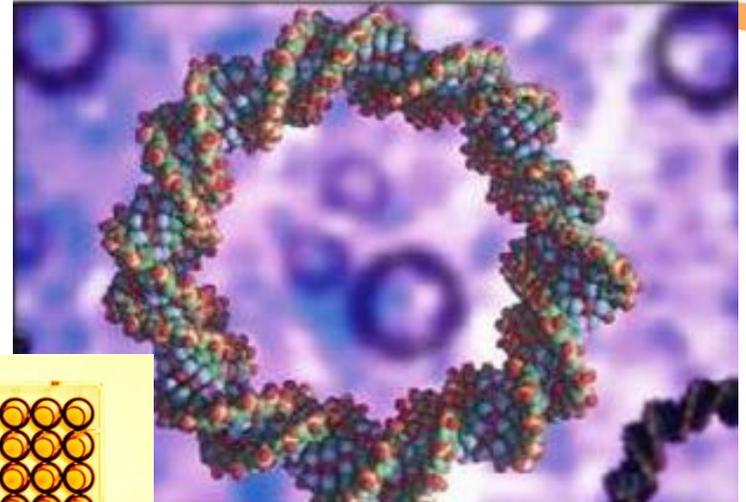
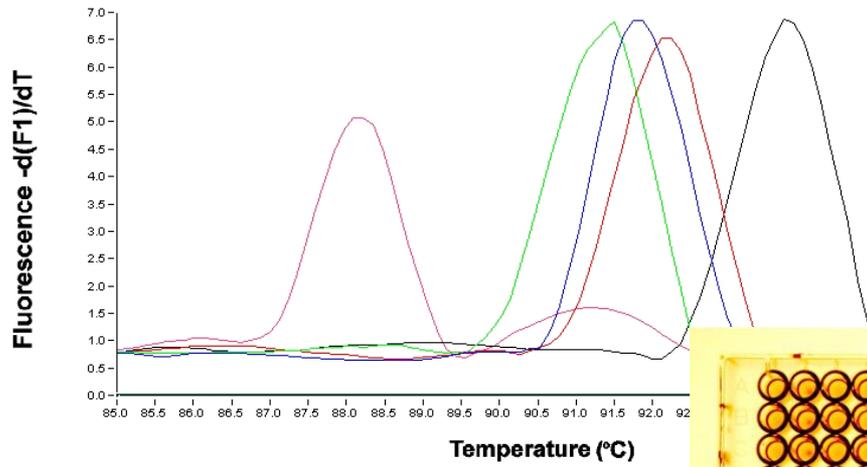


## Definition of the ESBL and/or AmpC producing bacteria and genes relevant for PH and linked to FP-animals or FB-transmission

- The predominant ESBL families are CTX-M, TEM, and SHV. The predominant AmpC-family is CMY. The most common ESBL genes in animals are *bla*<sub>CTX-M-1</sub>, and *bla*<sub>CTX-M-14</sub>, followed by *bla*<sub>TEM-52</sub> and *bla*<sub>SHV-12</sub>; the most common AmpC gene is *bla*<sub>CMY-2</sub>.
- The bacterial species most commonly identified with these genes are *E. coli* and non-typhoidal *Salmonella*.
- Phylogroup B2-*E. coli* O25:H4-ST131, phylogroup D-*E. coli* O25a-ST648 and phylogroup D- *E. coli*-ST69, -ST393, are being increasingly detected among both humans and animals. Among *Salmonella* the most common serovars are Typhimurium, Newport, and Heidelberg.
- ESBL/AmpC transmission is mainly driven by integrons, IS, Tn and plasmids, some of which are homologous in isolates from both FP-animals and humans.

- The prevalence of resistance to cefotaxime in FP-animals varies by country and species.
- Since 2000, the presence of ESBL- and/or AmpC-producing *Salmonella* and *E. coli* in animals and food has been increasingly reported (EU and globally). These have been described in all FP-animal species, but they are most frequent among poultry and derived products.
- Epidemic plasmids belonging to the Inc groups F, A/C, N, HI2, I1 and K carrying particular ESBL-encoding genes ( $bla_{TEM-52}$ ,  $bla_{CTX-M-1, -9, -14, -32}$ ) or AmpC-encoding genes ( $bla_{CMY-2}$ ) have been detected among farm and companion animals, food products and humans.

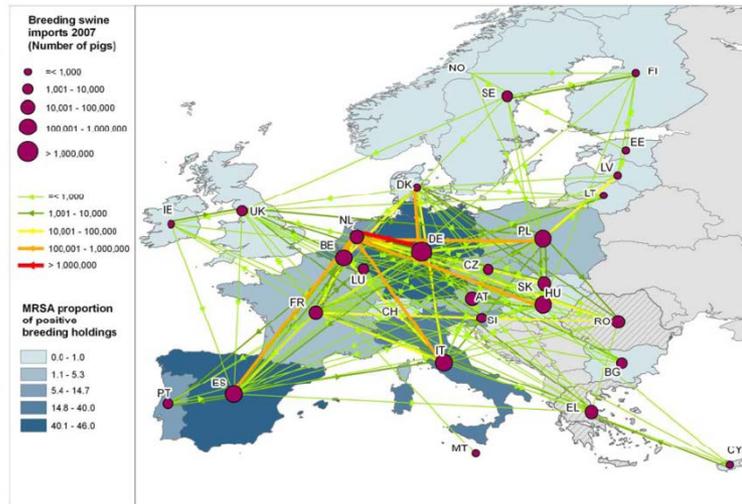
- A few studies describe clear evidence of direct transmission of ESBL or AmpC-producing *E. coli* isolates from FP-animals or food to humans. Indirect evidence for this transmission exists because of the finding of common clones in humans and FP-animals.
- Comparison of *E. coli* derived from humans and poultry has shown that AMR isolates from both reservoirs are more frequently genetically related than AMS isolates. Recent findings indicate transmission of ESBL genes, plasmids and clones from poultry to humans is most likely to occur through the food chain.
- There is limited evidence for spread of ESBL/AmpC-carrying organisms via direct contact with animals or indirectly via the environment. Nevertheless people working with poultry have a higher risk for intestinal carriage of ESBL/AmpC-producing bacteria.



# Methods for detection (isolation and identification) and characterisation of ESBL and/or AmpC-producing bacteria, genes and associated mobile elements (I)

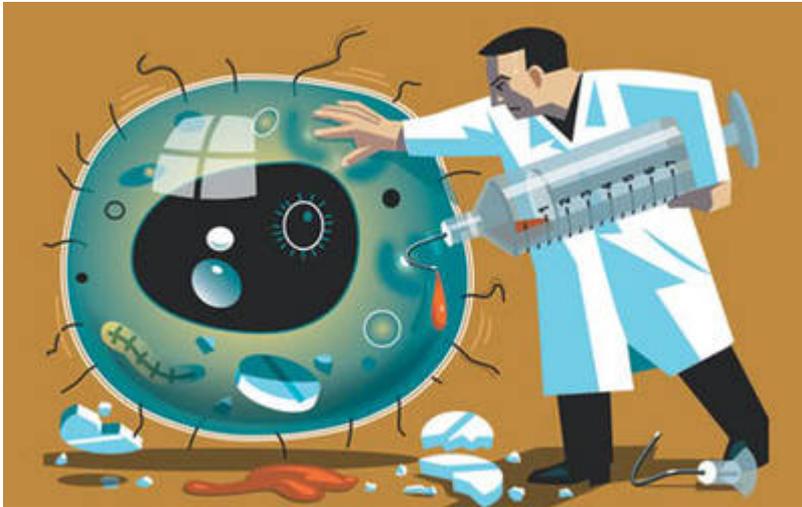
- The preferred method for isolation is **selective isolation** on agar preceded by selective enrichment in a broth. The preferred selective medium is chromogenic agar (e.g. MacConkey) with **1 mg/L cefotaxime or ceftriaxone**. Using low concentrations results in optimum sensitivity to detect all relevant  $\beta$ -lactamase families. Pre-enrichment may be performed in a general broth like MH, BHI or LB broth with 1 mg/L cefotaxime or ceftriaxone
- Identification is performed by determination of susceptibility to **cefotaxime, ceftazidime and cefoxitin**. ESBL-producers are resistant to cefotaxime, variably resistant to ceftazidime and susceptible to cefoxitin. Confirmation of ESBLs is performed by **testing for synergy** with clavulanic acid by combination disks, ESBL-e-tests or broth micro-dilution. Confirmation of AmpC producers is performed by determination of susceptibility to cefepime. AmpC producers are susceptible to cefepime and resistant to cefotaxime, ceftriaxone and cefoxitin.
- In order to harmonize the interpretation of susceptibility data, it is important to use **EUCAST clinical breakpoints** for interpretation of susceptibility or resistance and **EUCAST ECOFFs** to determine if an isolate belongs to the wild-type population or not.

- Isolates phenotypically confirmed to be either ESBL or AmpC-producers may be screened for  $\beta$ -lactamase gene families using **micro-array**, or **(multiplex) PCR**. The ESBL and/or AmpC subtypes may be identified by dedicated PCRs and **sequence analysis** of the amplicons.
- Characterization of plasmids on which  $bla_{ESBL}$  and/or  $bla_{AmpC}$ -genes are located is essential to study the epidemiology of this resistance. The plasmid can be typed using **replicon typing** and sub-typed by **fingerprinting** or **MLST**.
- Next to phenotypic methods such as serotyping, and phage typing, **PFGE** or **MLVA** can be used to identify clusters of isolates that are related to a certain 'outbreak' in a restricted time frame. **MLST** is generally the method of choice to identify relatedness of isolates of the same species from different backgrounds (e.g. animal *versus* human).



- The establishment of risk factors is particularly complicated by the data unavailability or lack of its accuracy.
- The **use of antimicrobials** is a risk factor for emergence and spread of resistant clones. Most ESBL- and AmpC-producing strains carry additional resistances such as to sulphonamides and other commonly-used veterinary drugs. Therefore, generic antimicrobial use is a risk factor for ESBL/AmpC and it is not restricted specifically to the use of cephalosporins.
- The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC), coordinated by EMA, is collecting information on the use of antimicrobials

- An extensive **trade of animals** occurs in EU MS, with few countries leading the production and the export, and with a small number of companies producing pure line grandparent stock. How widespread are ESBL-carrying bacteria in food-producing animals in the breeding/rearing/fattening sectors is generally unknown, although few reports suggest that ESBL/AmpC are not uncommon in the top of some production pyramids (breeding).
- ESBL- and/or AmpC-producing *E. coli* are disseminated in the poultry production chain through **day-old grandparent chickens**. Moreover, some data indicate that the occurrence of these organisms in the different levels of the poultry production chain is the result of vertical transmission, local recirculation and selection.



# COMBAT DRUG RESISTANCE



**No action today,  
no cure tomorrow**

7 APRIL 2011 WORLD HEALTH DAY  World Health Organization

There are no data on the comparative efficiency of individual control options in reducing PH risks caused by ESBL and/or AmpC-producing bacteria related to FP-animals. **Prioritisation is complex**, and the effectiveness of measures are based on the best available evidence and expert opinion.

- A highly effective control option to reduce selection of ESBL/AmpC-producing bacteria, would be to **stop all uses** of cephs/systemically active 3rd-4th generation cephs for FP-animals, or to **restrict their use** (use only allowed under specific circumstances).
- It is important to implement control measures covering all **off-label usage** of cephs in FP-animals.
- Measures intended to minimize off-label use of antimicrobials should focus on increased compliance with existing legislation.

- As **co-resistance** is an important issue, it is of high priority to **decrease the total antimicrobial use** in animal production in the EU.
- Also of importance (more so after resistance has emerged) are the measures to control dissemination, for example, by implementing increased farm **biosecurity** and **controls on animal trade** (of ESBL/AmpC carriers), by improving **hygiene** throughout the food chain, and by implementing other general **post-harvest controls** for food-borne pathogens.
- Because most evidence is available for high prevalence of ESBL/AmpC-producing bacteria in the **poultry production pyramid**, and their consequent involvement in public health, it is of high priority:
  - To reduce selection pressure (use of antimicrobials).
  - To prevent vertical transmission from the top of the poultry production pyramid.
  - To prevent local recirculation within subsequent flocks.

On **harmonised monitoring** of resistance caused ESBL- and/or AmpC-producing bacteria:

- Harmonised monitoring of resistance caused by ESBLs and AmpC will need to go beyond the existing recommendations for routine phenotypic surveillance. Specifically, **genotypic resistance testing** should be performed in addition to the phenotypic testing foreseen in the existing recommendations.
- For surveillance schemes, the analysis of isolates deriving from **passive surveillance** schemes (diagnostic submissions), from **systematic sampling**, and from **targeted surveys**, using **selective isolation methods and pre-enrichment of samples**, should be undertaken.



**EFSA Scientific Opinion on  
*Carbapenem resistance in food  
animal ecosystems***

- Self tasking mandate from EFSA in December 2012
- Scientific Opinion adopted by the BIOHAZ Panel in December 2013



European Food Safety Authority EFSA Journal 2013;11(12):3501

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**SCIENTIFIC OPINION**

**Scientific Opinion on Carbapenem resistance in food animal ecosystems<sup>1</sup>**

**EFSA Panel on Biological Hazards (BIOHAZ)<sup>2,3</sup>**

European Food Safety Authority (EFSA), Parma, Italy

**ABSTRACT**

Carbapenems are broad-spectrum  $\beta$ -lactam antimicrobials used for the treatment of serious infections in humans. To date only sporadic studies have reported the occurrence of carbapenemase-producing (CP) bacteria in food-producing animals and their environment. The bacteria and enzymes isolated include VIM-1 producing *Escherichia coli* and *Salmonella* Infantis from pigs and poultry in Germany, OXA-23-producing *Acinetobacter* spp. from cattle and horses in France and Belgium, and NDM-producing *Acinetobacter* spp. from pigs and poultry in China. In the German *S. Infantis* and *E. coli* isolates, the VIM-1-encoding genes were located on IncHI2 plasmids. A methodology including selective culture is proposed for the detection of CP strains of Enterobacteriaceae and *Acinetobacter* spp. The choice of selective media for the surveillance of carbapenem resistance for testing animal and food samples needs to be experimentally evaluated and validated. Biochemical and phenotypic tests for the confirmatory identification of CP bacteria are available. For CP bacteria in animals and food, active/passive monitoring and/or targeted surveys should cover key zoonotic agents, animal pathogens and indicator organisms. Priority should be given to broilers, fattening turkeys, fattening pigs, veal calves and meat thereof. Because there are no data on the comparative efficacy of individual control options, prioritisation is complex. Continued prohibition of the use of carbapenems in food-producing animals would be a simple and effective option. As genes encoding carbapenemase production are mostly plasmid-mediated, and co-resistance may be an important issue in the spread of such resistance mechanisms, decreasing the frequency of use of antimicrobials in animal production in the EU in accordance with prudent use guidelines is also of high priority. The effectiveness of any control measures should be monitored by targeted surveys, using selective isolation methods and pre-enrichment of samples. Control measures should be proactively implemented at national and international levels to prevent CP strains become widespread in livestock.

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**KEY WORDS**

- Carbapenems:
  - last-resort antimicrobials in the treatment of highly drug-resistant Gram-negative infections in humans
  - usually not included in panels of AMR national surveillance (at least until recently – Decision 2013/652/EU)
- Resistance to carbapenems:
  - results in loss of activity of nearly all beta-lactam antibiotics
  - recently reported in bacteria from animals in some EU MSs
  - new and potentially emerging problem in food-producing animals
- 2012 EFSA BIOMO Technical specifications on the harmonised monitoring and reporting of AMR recommended phenotypic testing for carbapenem resistance in *Salmonella* and *E. coli* to be performed consistently
- Actions to limit the spread of resistance are only possible when prevalence is low

1. Define the carbapenemase-producing bacterial **strains and genes** relevant for public health and **linked to food-producing animals or food-borne transmission**
2. Review the information on the **epidemiology** of acquired resistance to carbapenems, including the genes coding for such resistance, in food-producing animals and food
3. Perform a **critical analysis of the methods (phenotypic and genotypic)** and the interpretive criteria currently used for detection (isolation and identification) and characterisation of carbapenemase-producing bacterial strains
4. Make recommendations for the **harmonised monitoring and reporting** of resistance (phenotypic and genotypic) caused by carbapenemases in food and food-producing animals in the EU
5. Identify possible **means of preventing or minimising the further emergence and spread** of carbapenemase-producing bacterial strains transmitted via the food chain, including consideration of the advantages and disadvantages of different options

- Intrinsic resistance: different mechanisms due to intrinsic properties of bacteria (e.g. low permeability etc.)
- Acquired resistance: due to acquisition of exogenous genetic material containing gene(s) coding for the production of carbapenemases

**SCOPE OF THE OPINION**  
Carbapenemase-producing (CP) bacteria with acquired carbapenemases that could be transferred from food-producing animals and/or food thereof to humans directly/indirectly

- Variety of acquired carbapenemases described in humans in:
  - Enterobacteriaceae: *E. coli*, *Salmonella* spp., *Klebsiella pneumoniae*
  - *Acinetobacter* spp.
  - *Pseudomonas* spp.
- Risk factors for emergence of resistance to carbapenems:
  - Increased consumption of carbapenems (also as a result of spread of ESBLs in Enterobacteriaceae worldwide)
- Main concerns:
  - Few /no effective antimicrobials remain available
  - Mobile genetic elements encoding for resistance are highly transmissible
  - 40-50% in-hospital mortality rates

- Prevalence in humans:

- Largely unknown
- EU data reported in EARS-Net (invasive bacterial pathogens from bloodstream/CSF infections)
- US data from acute-care hospitals: increasing proportion of resistant isolates e.g. in *K. Pneumoniae* from 2001 (1.6%) to 2011 (10.4%)
- Other sporadic reports worldwide

(ECDC AMR surveillance in Europe, 2011)

Figure 4.12: *Klebsiella pneumoniae*: percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2011



# CP bacteria and public health relevance

- Several:
  - sources of CP bacteria described
  - enzymes produced

**Table 3:** Bacterial reservoirs of acquired carbapenemases of clinical importance and identified sources

Enzyme family	Functional group or subgroup	Molecular class	Target species	Representative enzymes	Source
GES	2f	A	Enterobacteriaceae, <i>Pseudomonas</i> spp., <i>Acinetobacter</i> spp.	GES-4, -5, -6, -11, -14	HH, WWTP
KPC	2f	A	Enterobacteriaceae, <i>Pseudomonas</i> spp.	KPC-2 to KPC-13	HH, HV, SW,
SME	2f	A	<i>Serratia marcescens</i>	SME-1 to SME-3	HH
IMI	2f	A	<i>Enterobacter</i> spp., <i>Escherichia coli</i>	IMI-1 to IMI-3	R, HH
NmcA	2f	A	<i>Enterobacter cloacae</i>	NmcA	HH
SFC	2f	A	<i>Serratia fonticola</i>	SFC-1	E
BIC	2f	A	<i>Pseudomonas fluorescens</i>	BIC-1	R
OXA	2df	D	<i>Acinetobacter</i> spp.	OXA-23 group (OXA-23, -27, -49)	AN, R, HV, head lice
		D	<i>Acinetobacter</i> spp.	OXA-24 group (OXA-25, -26, -40, -72)	HH
		D	<i>Acinetobacter</i> spp.	OXA-58 group (OXA-59, -164)	HH
		D	<i>Acinetobacter</i> spp.	OXA-143	HH
		D	<i>Acinetobacter</i> spp.	OXA-235	HH
		D	Enterobacteriaceae	OXA-48 group (OXA-48, -181, -204, -232)	HH, AN
		D	Enterobacteriaceae, <i>Pseudomonas</i> spp.	IMP-1 to IMP-33	HH, R
VIM	3a	B	Enterobacteriaceae, <i>Pseudomonas</i> spp., <i>Brevundimonas</i> spp., <i>Rhizobium</i> spp.	VIM-1 to VIM-34	HH, HV, AN, SW, R
NDM	3a	B	Enterobacteriaceae, <i>Pseudomonas</i> spp., <i>Acinetobacter</i> spp., <i>Vibrio</i> spp.	NDM-1 to NDM-8	HH, AN, SW, R
SPM	3a	B	<i>Pseudomonas aeruginosa</i>	SPM-1	HH
GIM	3a	B	<i>Pseudomonas aeruginosa</i>	GIM-1	HH
SIM	3a	B	<i>Acinetobacter baumannii</i>	SIM-1	HH
AIM	3a	B	<i>Pseudomonas aeruginosa</i>	AIM-1	HH
DIM	3a	B	<i>Pseudomonas stutzeri</i>	DIM-1	HH
KHM	3a	B	<i>Citrobacter freundii</i>	KHM-1	HH
TMB			<i>Achromobacter xylosoxydans</i>	TMB-1	HH
FIM	3a	B	<i>Pseudomonas aeruginosa</i>	FIM-1	HH

HH = hospitalized patients; HV = healthy human; AN = animal; SW = sewage; WWTP = wastewater treatment plant; R = rivers; E = environment

1. Define the carbapenemase-producing bacterial **strains and genes** relevant for public health and **linked to food-producing animals or food-borne transmission**
2. Review the information on the **epidemiology** of acquired resistance to carbapenems, including the genes coding for such resistance, in food-producing animals and food.
  - Review of the scientific information available on CP microorganisms, genes encoding for carbapenemases, mobile genetic elements involved in transmission of resistance to carbapenems
  - Review of data on the occurrence of carbapenem resistance in animals and food thereof

Bacteria	Source	Enzyme	Location
Acinetobacter genomospecies 15TU	cattle	OXA-23	France
Acinetobacter spp.	chicken		China
Acinetobacter spp.	pig carcass		China
Actinetobacter lowffii	chicken	NDM-1	China
A. baumannii	pig	NDM-1	China
Acinetobacter spp.	horses	OXA-23	Belgium
putative Salmonella Infantis	pig farm	VIM-1	Germany
putative Salmonella Infantis	broiler farm	VIM-1	Germany
E. coli	pig farm	VIM-1	Germany
S. Corvallis	wild black kite	NDM	Germany
S. Cubana	human	KPC-2	USA
S. Saintpaul	human	OXA-48	France (Egypt)
S. Kentucky	human	VIM-2, OXA-48	France (Egypt)
S. Kentucky	human	OXA-48	Germany (Morocco)
S. Wetshampton	human	NDM-1	USA (India)
S. Senftenberg	human	NDM-1	USA
K. Pneumoniae	human	NDM-1	USA

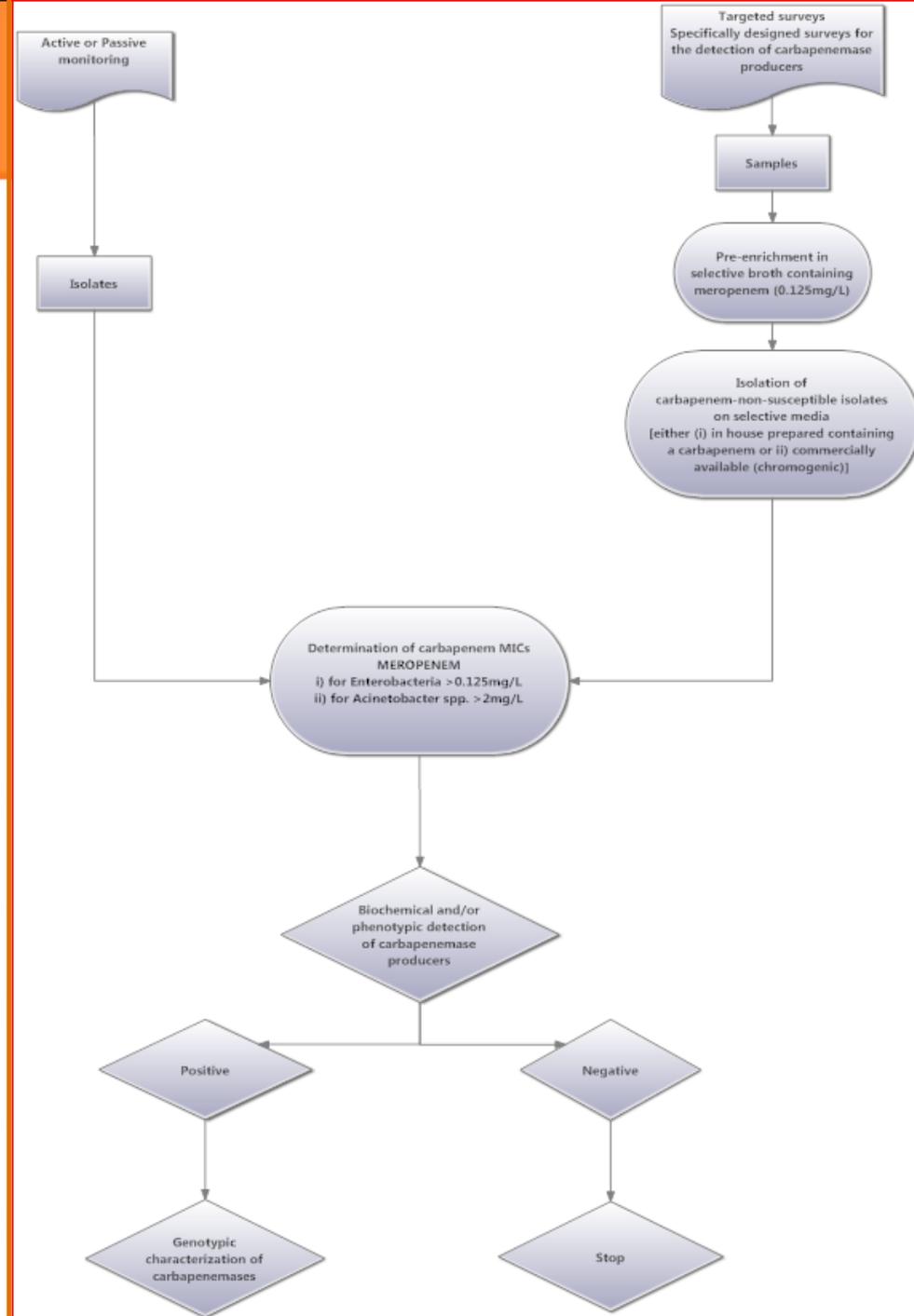
- Additional conclusions of the Opinion:
  - Harmonised monitoring of carbapenemase-producing bacteria in food-producing animals has as yet not been undertaken in the EU. EU-wide validated data on the occurrence of such resistance are therefore not available.
  - Transmission of carbapenemase-producing strains and/or resistance genes to humans through the food animal production environment or food chain has as yet not been reported, but is considered likely should these strains/genes spread more widely in food-producing animals.
  - Few studies have reported the presence of carbapenemase-producing bacteria in food-producing animals and their environment. Genes identified have included *bla*<sub>VIM-1</sub> in Enterobacteriaceae and *bla*<sub>NDM-1</sub> and *bla*<sub>OXA-23</sub> in *Acinetobacter* spp. No such carbapenemase-producing isolates have been identified in food derived from food-producing animals.
  - Carbapenemase-producing isolates belonging to *Salmonella* Cubana, *S. Kentucky*, *S. Saintpaul*, *S. Senftenberg* and *S. Westhampton* producing KPC-2, VIM-2, OXA-48 or NDM-1 have been recovered from cases of human infection, although the origin of the genes (animal, environmental or clinical settings) cannot be determined. All these serovars are regarded as potentially zoonotic in origin.

3. Perform a **critical analysis of the methods (phenotypic and genotypic)** and the interpretive criteria currently used for detection (isolation and identification) and characterisation of carbapenemase-producing bacterial strains.

- Review of methodologies and of materials (e.g. screening media) available for isolation and identification of CP bacteria in animals and humans
- Consideration to *EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance*
- Development and proposal of a methodology for the detection of CP strains of Enterobacteriaceae and *Acinetobacter* spp. in food-producing animals, their environment, food thereof
- Differentiation for active/passive monitoring vs. targeted surveys

# Answer to ToR 3

- **Targeted surveys** to detect CP producers **recommended**
  - **Pre-enrichment** step in broth containing **meropenem**
  - Determination of MICs:
    - for **meropenem**
    - based on epidemiological cut-off (**ECOFF**), as opposed to clinical breakpoints
- = carbapenem non-susceptible
- Detection of carbapenemase producers
  - Characterisation of carbapenemases



- Use of meropenem: good balance between sensitivity and specificity
- Use of ECOFF: sets a stricter target with the aim of detecting CP strains, not based on response to clinical treatment
- Opinion provides review of:
  - commercial and in-house prepared selective media available
  - methods for phenotypic and biochemical detection of CP producers
  - methods for characterisation of carbapenemases and typing of plasmids carrying genes encoding for the production of carbapenemases

- Additional conclusions of the opinion:
  - A methodology including selective culture is proposed for the detection of carbapenemase-producing strains of Enterobacteriaceae and *Acinetobacter* spp.
  - **Pre-enrichment** by incubation of samples in selective broth containing a carbapenem at a low concentration (e.g. meropenem 0.125 mg/L) may increase sensitivity. **This methodology has not yet been validated, and any method proposed would have to be subjected to thorough experimental verification.**
  - A variety of in-house and commercially-available **selective media** has been used for the active surveillance of carbapenem resistance in hospitals. **The choice of the media for testing animal and food samples needs to be experimentally evaluated and validated.**
  - Meropenem offers a good balance between sensitivity and specificity and has been recommended to be included in the harmonised antimicrobial panel for the surveillance of AMR in isolates from food-producing animals, food thereof and environmental samples.
  - **Biochemical and phenotypic tests** for the confirmatory identification of carbapenemase-producing bacteria among isolates exhibiting non-susceptibility to carbapenems are available. **The sensitivity and specificity of these assays may vary considerably in different settings.**
  - **The identity of the genes responsible for the carbapenemase production should be determined** by molecular methods.
  - **Plasmid and strain typing should be undertaken to acquire better knowledge on the epidemiology of genes encoding carbapenemase production** among bacteria from food-producing animal populations, food thereof and environmental samples.

## 4. Make recommendations for the **harmonised monitoring and reporting** of resistance (phenotypic and genotypic) caused by carbapenemases in food and food-producing animals in the EU.

- Purposes are to obtain information on:
  - ✓ presence/prevalence of carbapenem non-susceptible (CNS) bacteria in food-producing animals and food (EU and imported)
  - ✓ geographical distribution of CNS bacteria within the EU
  - ✓ detect changes in presence/prevalence over time
  - ✓ detect CP bacteria amongst CNS bacteria
  - ✓ identify genes responsible for CP
  - ✓ detect emergence of new carbapenemase-encoding genes with potential relevance to public health
  - ✓ determine the effect of interventions on the prevalence of carbapenemase-mediated resistance

- Review of:
  - options for monitoring: active monitoring, passive monitoring, targeted surveys
  - sampling design
  - sampling size
- Some conclusions of the Opinion:
  - **Requirements for the collection and reporting** of antimicrobial resistance data, including resistance to carbapenems, **are laid down in European legislation.**
  - **Since some carbapenemase-producing strains have been identified in food animals and their environment, more detailed investigation is now required to determine the extent and distribution of such strains in the food animal ecosystem.**
  - **Active monitoring and/or additional targeted surveys** for carbapenemase-producing bacteria in animals and food **should cover key zoonotic agents and indicator organisms** of the commensal flora. **Priority should be given to broilers, fattening turkeys, fattening pigs, veal calves, and the derived fresh meat of domestic origin. Dairy cattle, raw milk and aquaculture products may be also included in targeted surveys.**

- Some conclusions of the Opinion:
  - For **active monitoring**, all isolates of *Salmonella* spp. and *E. coli* collected within the compulsory monitoring programme, as required by European legislation, **should be screened for meropenem resistance** using standardized microdilution methods.
  - For **passive monitoring, diagnostic isolates of veterinary origin** (at least those classified as microbiologically resistant to 3rd- or 4th-generation cephalosporins on the basis of epidemiological cut-off values) **should be subjected to phenotypic testing for carbapenem resistance and carbapenemase production, and subsequent molecular identification and characterization of the carbapenemase production genes present.**
  - **Methods involving pre-enrichment and selective plating should be used in specific surveys to increase sensitivity** for populations with a low prevalence of carbapenemase-producing microorganisms.
- Additional recommendation:
  - **Fruit and vegetables**, particularly those which are more prone to bacterial contamination and are usually consumed raw, should be assessed for contamination with bacteria with acquired carbapenemases.

5. Identify possible **means of preventing or minimising the further emergence and spread** of carbapenemase-producing bacterial strains transmitted via the food chain, including consideration of the advantages and disadvantages of different options.

- Public health **risks** linked to CP bacteria due to:

- Prevalence/concentration of CP bacteria in food-producing animals and food
- Genetic characteristics of genes involved



- Frequency/ magnitude of transmission from food-producing animals/food to humans



- Focus of the **control measures**:

- Preventing introduction in food-producing animals
- Reducing prevalence/concentration

- Reducing transmission

- Conclusions of the Opinion:

- Because there are no data on the comparative efficacy of individual control options in reducing the potential public health risks caused by carbapenemase-producing bacteria related to food-producing animals, prioritisation is complex.
- All efforts should be made to continue to regard carbapenems as Critically-Important Antimicrobials that should be reserved specifically for the treatment of serious infections with multidrug-resistant bacteria in humans, and not used in food-producing animals.
- As carbapenems are not licensed for use in food-producing animals in the EU and other parts of the world, one simple and effective control option to minimise the further emergence and possible spread of such strains transmitted *via* the food chain would be to continue to prohibit the use of carbapenems in food-producing animals.
- As already stated for reducing ESBL/AmpC resistance, restriction of usage of cephalosporins/ systemically active 3<sup>rd</sup>/4<sup>th</sup> generation cephalosporins to very specific circumstances and prohibition of off-label use might be a highly effective control option to reduce selection pressure.

- Conclusions of the Opinion:

- As long as findings of carbapenemase-producing strains are rare events in food-producing animals, **each positive finding should be thoroughly investigated.**
- As genes encoding carbapenemase production are mostly plasmid-mediated, and co-resistance may be an important issue in the spread of such plasmid-mediated resistance mechanisms, **decreasing the frequency of use of antimicrobials in animal production in the EU in accordance with prudent use guidelines** is also of high priority.
- **The effectiveness of any control measures should be monitored on a regular basis by targeted surveys of food-producing animals and foods for carbapenemase-producing bacteria,** using selective isolation methods and pre-enrichment of samples as necessary.
- Control measures to contain the spread of carbapenemase-producing bacteria in food-producing animals should be proactively implemented at national and international levels, and should involve **inter-departmental communication between human and veterinary authorities.** Such plans should be agreed to prevent carbapenemase-producing strains become widespread in livestock.

# A few key messages...

- Resistance to carbapenems is an emergent and highly sensitive public health issue, since it could leave few available therapeutic options for human patients
- So far only a few studies have reported carbapenem-resistant bacteria in food-producing animals and none in derived food
- Transmission of carbapenemase-producing bacteria or resistance genes through the food chain has not been reported but is considered likely
- Specific targeted surveys should be conducted at EU level
- Measures to prevent and minimising further emergence of this resistance need to be taken

# Thank you for your attention!

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